Multicenter, Randomized, Open-Label Study of OROS Methylphenidate versus Atomoxetine: Treatment Outcomes in African-American Children with ADHD

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The Formal Observation of Concerta® versUs Strattera® (FOCUS) study was conducted to assess, in children with ADHD, treatment outcomes with Concerta [OROS methylphenidate (MPH)], a once-daily controlled-release medication, and Strattera, (atomoxetine), a selective noradrenaline reuptake inhibitor. Because of the lack of data in minority groups treated for ADHD, the present subgroup analysis was conducted to determine the effectiveness and tolerability of ADHD treatments in African-American patients who were randomized to OROS MPH (n=125) or atomoxetine (n=58) during the FOCUS study. At the end of the study, the mean dose of OROS MPH was 32.8 ± 10.9 mg and that of atomoxetine was 1.1 ± 0.4 mg/kg. The results demonstrated that both treatments were associated with significant improvements in ADHD symptoms from baseline; however, patients who received OROS MPH demonstrated significantly greater improvements in total ADHD symptoms, inattentiveness and global improvement. The incidence of adverse events was similar in both treatment groups. OROS MPH and atomoxetine are effective and tolerable in the treatment of African Americans with ADHD, and significantly greater treatment responses were observed in patients receiving OROS MPH compared with those receiving atomoxetine over three weeks. Additional studies are needed to evaluate treatment response in this population.

Key words: attention-deficit disorder with hyperactivity ■ methylphenidate ■ atomoxetine ■ African Americans

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INTRODUCTION

The most studied and most often used stimulant medication for attention-deficit/hyperactivity disorder (ADHD) is methylphenidate (MPH).[1] By 1996, there were 133 randomized, controlled trials describing the treatment of ADHD with MPH.[2] However, MPH has a short duration of effect that results in a need for multiple daily dosing. Therefore, several long-acting formulations have been developed to minimize the need for repeated daily dosing. One such formulation of MPH uses OROS, technology (OROS MPH) to allow for once-daily dosing. The OROS MPH (Concerta®) formulation has been shown to be safe and effective during short-term, double-blind, controlled trials.[3,4] In addition, interim results from an open-label, long-term study of OROS MPH reported that efficacy is maintained over 12 months and that OROS MPH was associated with significant improvements in symptoms of treatment-naïve patients, according to ratings by caregivers and teachers.[5]

Atomoxetine, a selective noradrenaline reuptake inhibitor, is the first nonstimulant medication for the treatment of ADHD.[6] The precise mechanism of action is not known, but it is thought that the efficacy of atomoxetine might relate to increasing noradrenergic transmission in cortical areas. Six published studies have reported that atomoxetine was effective in decreasing ADHD Rating Scale (ADHD-RS) scores and Clinical Global Impression–Severity of Illness (CGI-SI) scores from baseline in children and adolescents; however, these trials excluded patients with most comorbid psychiatric diagnoses, patients who were receiving psychotropic medications and substance abusers.[6-12]

This subgroup analysis was conducted to evaluate the effectiveness and tolerability of OROS MPH and atomoxetine in African-American children who participated in the Formal Observation of Concerta® versUs Strattera® (FOCUS) study,[13] which was conducted in 1,323 children with ADHD to evaluate treatment outcomes with OROS MPH and atomoxetine.

METHODS

Patients

Eligible children were 6–12 years of age with a diagnosis of ADHD based on psychiatric history and a review of the DSM-IV diagnostic checklist. Children must have scored ≥24 on the ADHD-RS[14] at screening and must have been rated "moderately ill" or worse on the CGI-SI.[15] Newly diagnosed treatment-naïve patients and previously diagnosed patients who were previously taking some type of ADHD medication but who may not have been receiving adequate treatment as judged by the clinician in conjunction with the parents were eligible for inclusion. Female patients who had experienced menarche were excluded. Patients also were excluded if they had an eating or substance use disorder; a comorbid psychiatric condition other than oppositional defiant disorder; a history of seizures, tic disorder, mental retardation, severe developmental disorder or family history of Tourette's syndrome; or hyperthyroidism or glaucoma. In addition, patients were excluded if they were receiving a medication that is contraindicated during treatment with OROS MPH or atomoxetine, or if they did not respond to prior treatment for ADHD.

Study Design

This large, multicenter, randomized, open-label, community-based study was conducted among 323 sites. Patients receiving drug therapy for ADHD at enrollment must have discontinued the medication for the greater of three days or five drug half-lives. Eligible patients were randomized in a 2:1 fashion to receive OROS MPH or atomoxetine once daily for 21 days. To directly mimic clinical practice, investigators determined if the starting daily doses of OROS MPH (18 mg) and atomoxetine (0.5 mg/kg) were to be maintained or titrated to higher levels based on assessments made during study visits. Treatment adherence was recorded throughout the study by formal query at each parent/patient contact.

This study was conducted in accordance with the Declaration of Helsinki and its amendments. Written informed consent or assent was obtained from each patient and parent or guardian before enrollment. An independent, centralized institutional review board reviewed and approved the study protocol prior to the start of the study.

Outcome Measures

Investigators used the Clinical Global Impression–Improvement of Illness (CGI-I) and the ADHD-RS to evaluate effectiveness. The CGI-I is a single rating of improvement that is scored on a seven-point scale (1 = very much improved, 7 = very much worse). The ADHD-RS is the sum of 18 behavioral status scores, which are rated on a scale from 0 (never or rarely) to 3 (very often). The ADHD-RS and the CGI-SI or CGI-I were completed at baseline, by phone (during week 1) and during study visits at weeks 2 and 3. All investigators were chosen on the basis of their extensive experience evaluating and treating patients with ADHD and because their practice sites included a large patient base with ADHD. Prior to the study, all investigators were trained on the use of study instruments using a web-based training course.

Parents evaluated treatment outcomes using the Parental Satisfaction Questionnaire (PSQ) to rate aspects of the patient's behavior on a five-point scale from "strongly agree"

Table 1. Demographics and baseline disease characteristics in African-American patients treated with OROS MPH or atomoxetine

	OROS MPH (n=125)	Atomoxetine (n=58)	Total (N=183)
Age (years)*	8.6 (2.0)	9.1 (2.2)	8.8 (2.0)
Gender (%)			
Male	80	86	82
Female	20	14	18
Predominant Type (%)			
Hyperactive-impulsive	12.1	18.5	14.1
Inattentive	9.8	8.0	9.1
Combined	16.2	12.0	14.7
Family history of ADHD (%)	46	49	47
Prior treatment for ADHD (%)	45	69	52
Duration of ADHD, mo*	23.5 (23.5)	33.2 (28.4)	27.0 (25.7)
ADHD-RS*	40.4 (8.3)	40.9 (8.7)	40.6 (8.4)
CGI-SI*	4.9 (1.0)	4.9 (1.0)	4.9 (1.0)

* Mean values (SD); ADHD: attention-deficit/hyperactivity disorder; ADHD-RS: Attention-Deficit/Hyperactivity Disorder Rating Scale; CGI-SI: Clinical Global Impression–Severity of Illness

to "strongly disagree." Other PSQ statements were rated on a five-point scale from "better than" to "worse than" or as "yes" or "no." The PSQ was collected daily on days 2–13 and at weeks 2 and 3. The sum of PSQ scores was to be analyzed.

Safety was evaluated by monitoring adverse events, vital signs and body weight. Adverse event monitoring began from the time patients entered the study until the final visit. Study personnel assessed the incidence of adverse events by phone during week 1 and during study visits at weeks 2 and 3 by querying patients to determine the emergence or presence of adverse events. In addition, patients were instructed to immediately report all adverse events to the study center regardless of causality. Study personnel recorded all adverse events. Serious adverse events were defined as those that required hospitalization, prolonged existing hospitalization, resulted in persistent or significant disability or incapacity, were life-threatening or resulted in death or an important medical event. The severity of adverse events was graded as mild, moderate or severe. Investigators assessed the seriousness, clinical severity and relationship of adverse events to study drugs.

Statistical Analysis

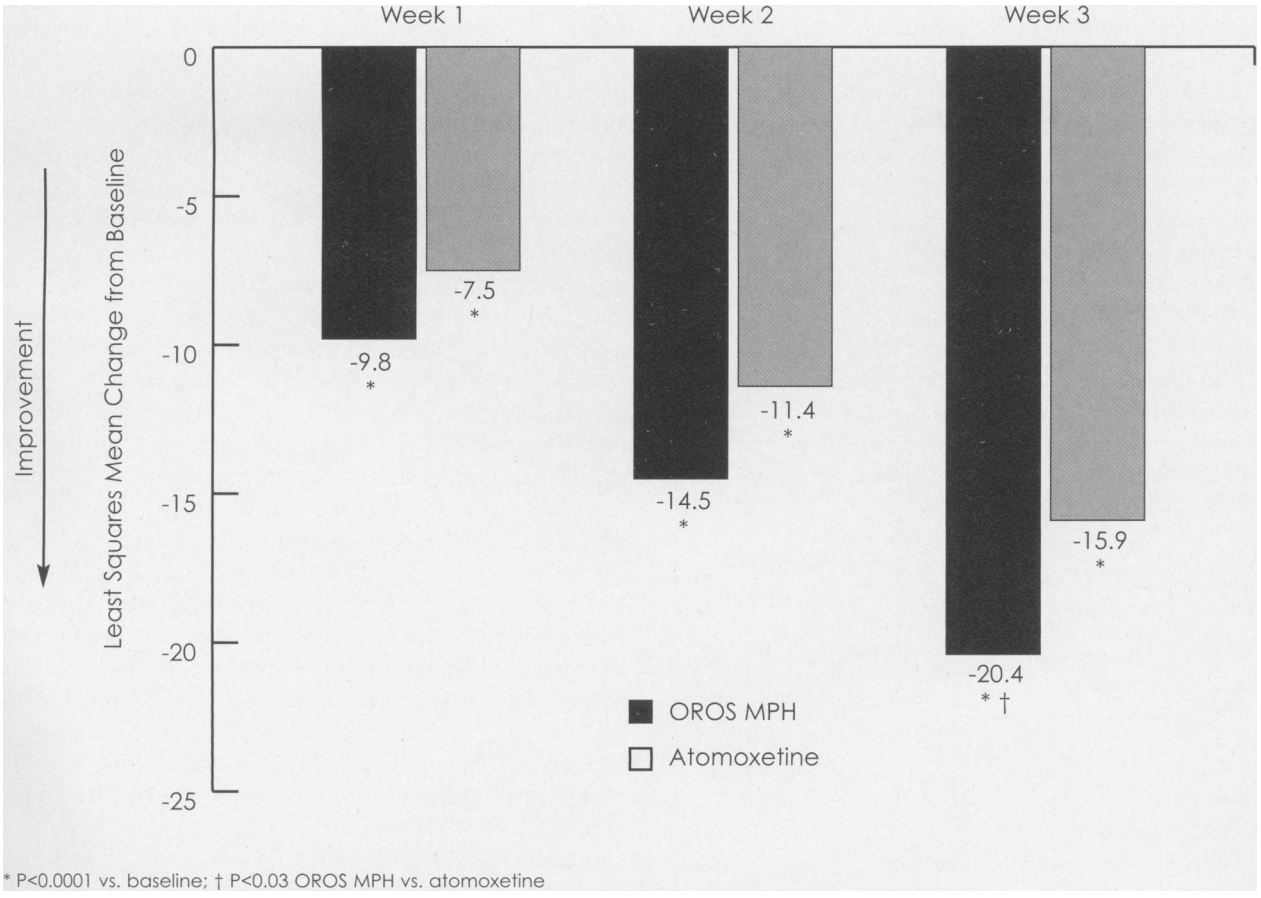
Descriptive statistics and frequency distributions were used to summarize demographic variables, disease history, baseline characteristics and change from baseline behavior. Analysis of covariance was used to analyze data when baseline values were used as a covariate with treatment as the between-patient factor and visit as a repeated factor. Treatment effects were tested by Chi-squared statistics.

RESULTS

A total of 1,323 patients were enrolled in this study; of these, 183 were African-American (OROS MPH: n=125, atomoxetine: n=58).[6] The mean age of the total African-American group was approximately nine years, and most (87%) patients were male (Table 1). The treatment groups were well matched with regard to baseline disease characteristics. Adherence to study medication was high throughout the study and ranged 89.1%–97.9% in both groups. At the end of the study, the mean doses of OROS MPH and atomoxetine were similar between African-American (32.8 ± 10.9 mg, 1.1 ± 0.4 mg/kg, respectively) and non-African-American patients (32.7 ± 12.3 mg, 1.1 ± 0.4 mg/kg, respectively).

Both treatments were associated with significant improvements (P<0.0001) from baseline in total ADHD-RS scores at each week (Figure 1). All changes in the total ADHD-RS were greater in the OROS MPH group compared with the atomoxetine group and, during each successive week

Figure 1. Change from baseline in total Attention-Deficit/Hyperactivity Disorder Rating Scale score



of the study, the relative differences in improvement between treatments increased (week 1: difference of 2.3, week 2: difference of 3.1, week 3: difference of 4.5). A significant difference was observed between groups at week 3 ($P<0.03$). Both treatments were associated with significant improvements ($P<0.0001$) from baseline on the Inattentive Subscale and the Hyperactivity Subscale. However, each week, the OROS MPH group experienced greater improvement in both subscales; during the final week of the study, the improvement on the Inattentive Subscale was significantly greater in the OROS MPH group, compared with the atomoxetine group ($P<0.02$). In addition, at week 3, a significantly greater number of patients who received OROS MPH experienced ADHD-RS score reductions of ≥30% or ≥50% from baseline, compared with the atomoxetine group (≥30% reduction: 77.4% vs. 61.1%, respectively, $P<0.03$; ≥50% reduction: 58.3% vs. 35.2%, respectively, $P<0.006$). At week 3, CGI-I scores ≤2 (i.e., "very much improved" or "much improved") were observed in a significantly greater number of patients in the OROS MPH group (68.4%), compared with the atomoxetine group (49.1%) ($P<0.01$). Due to the difficulty in detecting significant differences between two active treatments and the relatively low number of patients available for this subanalysis (OROS MPH: n=125, atomoxetine: n=58), the differences between the experimental groups did not reach statistical significance until the final week of titration.

The PSQ data were consistent with those of the investigators and demonstrated a significantly greater improvement of ADHD symptoms in the OROS MPH group (total PSQ score = 19.8), compared with the atomoxetine group (total PSQ score = 23.4) ($P<0.009$). At the final visit, the percentage of parents stating that their child was doing "better than" or "somewhat better than" before treatment was 85.1% in the OROS MPH group and 63.8% in the atomoxetine group. These data were consistent with the other PSQ ratings.

The incidence of adverse events was similar between the African-American groups (Table 2). Treatment-related adverse events were reported in 19.2% of the OROS MPH group and in 19% of the atomoxetine group. The most common treatment-related adverse events included abdominal pain, decreased appetite and headache in the OROS MPH group; those in the atomoxetine group included somnolence, sedation and nausea. A slightly greater percentage of patients in the atomoxetine group (1.7%) compared with the OROS MPH group (0.8%) withdrew from the study because of adverse events. One serious adverse event (described as prolonged crying and fears of death for self and family), which resolved upon treatment discontinuation, was reported in a patient who received atomoxetine. No deaths were reported.

Table 2. Summary of treatment-related adverse events in ≥4% of children with ADHD

	OROS MPH	Atomoxetine
	n (%)	n (%)
Upper abdominal pain	6 (4.8)	1 (1.7)
Decreased appetite	5 (4.0)	1 (1.7)
Headache	5 (4.0)	1 (1.7)
Insomnia	4 (3.2)	0
Nausea	1 (0.8)	2 (3.4)
Somnolence	1 (0.8)	3 (5.2)
Sedation	0	3 (5.2)

ADHD: Attention-deficit/hyperactivity disorder

DISCUSSION

This was the first randomized study to directly compare OROS MPH and atomoxetine in African-American children. Response in this population was consistent with that observed in the overall population. Both treatments demonstrated significant improvement from baseline; however, improvements noted in the OROS MPH group were consistently greater than those observed in the atomoxetine group. Differences in improvements between the groups were significant at week 3, as measured by total ADHD-RS, the Inattentive Subscale and CGI-I scores. These data suggest that OROS MPH may be more effective than atomoxetine. In addition, it is worthwhile to note that some differences in effectiveness between treatment groups became greater as the study progressed. The reasons for this finding are not known. During a placebo-controlled study of atomoxetine in patients with ADHD, most of the treatment effects were exerted by the third week of treatment, with little additional improvement observed beyond this time period.[16] For this reason, the 21-day treatment period was chosen during the present study. The mean doses of atomoxetine during the placebo-controlled study (1.3 mg/kg/day) and the present study (1.1 mg/kg/day) were similar. According to the product information for atomoxetine, no additional benefits are observed beyond a mean daily dose of 1.2 mg/kg.[17]

Another study done predominately in white children with ADHD compared atomoxetine with an immediate-release formulation of MPH over 10 weeks; comparable outcomes were reported in patients who received either treatment.[18] However, it is not possible to make direct comparisons between that study and the present trial because each was unique in its design and patient population, and each tested a different MPH formulation. Because direct comparative studies are lacking, effect size calculations may be useful in comparing responses to stimulant and nonstimulant treatments evaluated during independent randomized, double-blind, placebo-controlled studies. According to effect size analyses, stimulant treatments, such as OROS MPH, are more likely to be effective in the management of ADHD than nonstimulant treatments.[19,20] The effect size of long-acting stimulant medications has been reported to be 0.95, whereas that of nonstimulant medications was reported as 0.62.[20] Another study that compared data from large, placebo-controlled studies of patients treated with OROS MPH or atomoxetine found that effect sizes from parent and teacher evaluations in patients treated with OROS MPH were 1.02 and 0.96, respectively, compared with 0.62 and 0.44, respectively, for atomoxetine.[19] In the present study, the difference in effect sizes for OROS MPH and ato-

moxetine for investigator-rated ADHD-RS in the African-American patients was calculated as 0.59, in favor of OROS MPH over atomoxetine. Differences greater than 0.2 are considered clinically important.[21]

No significant differences were noted between African Americans and non-African Americans for change from baseline in total ADHD-RS score, Inattentive Subscale or Hyperactivity Subscale scores in patients who received OROS MPH or atomoxetine. This study was not designed prospectively to determine significant differences in effectiveness between African-American patients and the non-African-American population; however, numerically similar improvements were observed between the groups in all outcome measures. Together with findings from other investigators, this implies that the clinical efficacy of ADHD treatment is similar between African-American and white children. One study used data from the highly controlled, double-blind MTA MPH trial[22] to explore the effect of ethnicity or race on clinical outcomes.[23] The study included African Americans and white children who were well matched for treatment, study site and gender. Response to MPH was reported in 76% (28/37) of African-American children and in 78% (29/37) of white children who received medication alone or in combination with behavioral therapy. Of note, the mean final dose of MPH was approximately 50% higher in the African-American group (48.7 mg/day), compared with the white group (32.4 mg/day). The investigators speculated that the need for increased doses in African-American children might be associated with the development of tolerance. However, this hypothesis was negated by the fact that African-American patients who received combined treatment (MPH and behavioral therapy) received MPH doses similar to those given to white patients.

Several limitations of this study should be considered. For example, the open-label study design may have caused investigator or patient bias that could have influenced outcomes. In addition, because this study did not include a placebo control group, secular trends cannot be ruled out as an alternative explanation of the changes from baseline. However, the differential effects between the two treatments cause this to be unlikely. A further limitation may be related to the disease characteristics of the treatment groups. Although the severity of ADHD as measured by the ADHD-RS was comparable between the groups at baseline, the duration of ADHD was greater in the atomoxetine group, compared with the OROS MPH group. This is difficult to explain, since the groups were randomized. The brief duration of the study may also be considered a limitation; however, the increased trend over time towards greater symptom improvement in patients who received OROS MPH, compared with that of those who received atomoxetine, suggested the study period was adequate. Still, it is possible that the full effects of atomoxetine are not observed in some patients during a three-week treatment period. Furthermore, the study was not powered prospectively to study the African-American subgroup; therefore, these data should be considered exploratory in nature.

CONCLUSION

Both OROS MPH and atomoxetine demonstrated improvement in baseline symptoms and similar incidences of adverse events in the treatment of ADHD in African-American children. These findings support the use of ADHD treatment in African-American patients with ADHD. The greater response to OROS MPH than atomoxetine at three weeks as reported by parents and investigators suggests that OROS MPH may be more effective than atomoxetine in the treatment of ADHD in African-American children.

Few studies have evaluated the treatment of ADHD in children who are members of minority groups.[24] An early, small study of 11 male African-American adolescents with ADD found that MPH exerted improvement in attention and impulsivity, with a linear dose effect. This small study also found a trend for an increase in side effects with increasing MPH doses, including a mean increase in diastolic blood pressure, which was noted to be within the normal pediatric blood pressure range.[25] Modest increases in blood pressure have also been noted with the use of atomoxetine.[9,11] Additional long-term studies are therefore warranted to study these treatments in larger populations.

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